Autonomic Dysfunction in Alzheimer's Disease: Tools for Assessment and Review of the Literature

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Review

Autonomic Dysfunction in Alzheimer's Disease: Tools for Assessment and Review of the Literature

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Abstract. Autonomic dysfunction is very common in patients with dementia, and its presence might also help in differential diagnosis among dementia subtypes. Various central nervous system structures affected in Alzheimer's disease are also implicated in autonomic nervous system regulation, and it has been hypothesized that the deficit in central cholinergic function observed in Alzheimer's disease could likely lead to autonomic dysfunction. Several feasible tests can be used in clinical practice for the assessment of parasympathetic and sympathetic functions, especially in terms of cardiovascular autonomic modulation. In this review, we describe the different tests available and the evidence from the literature which indicate a definite presence of autonomic dysfunction in dementia at various degrees. Importantly, the recognition of dysautonomia, besides possibly being an early marker of dementia, would help prevent the disabling complications which increase the risk of morbidity, institutionalization, and mortality in these individuals.

Keywords: Alzheimer's disease, autonomic nervous system, baroreflex, functional recovery, orthostatic hypotension

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide. AD affects more than 20% of individuals over 80 years of age, and its prevalence is expected to rise with the increase of life expectancy. However, there is still a limited understanding of this disease and its underlying causes, and existing drugs only provide symptomatic benefits but there are no currently available disease-modifying therapies [1]. It is now established that the two major protein abnormalities in AD brain pathology are amyloid-β (Aβ) deposition and tau accumulation. Besides these, other mechanism might contribute to sporadic AD, such as those suggested by the vascular hypothesis, which states that cardiovascular diseases are an important causal or contributing factor in AD, with hypertension regarded as the most powerful vascular risk factor for AD (Fig. 1) [2, 3]. Indeed, cardiovascular factors are commonly recognized as risk factors for AD, however, the relationship between cardiovascular factors and AD-related neurodegeneration is not clearly

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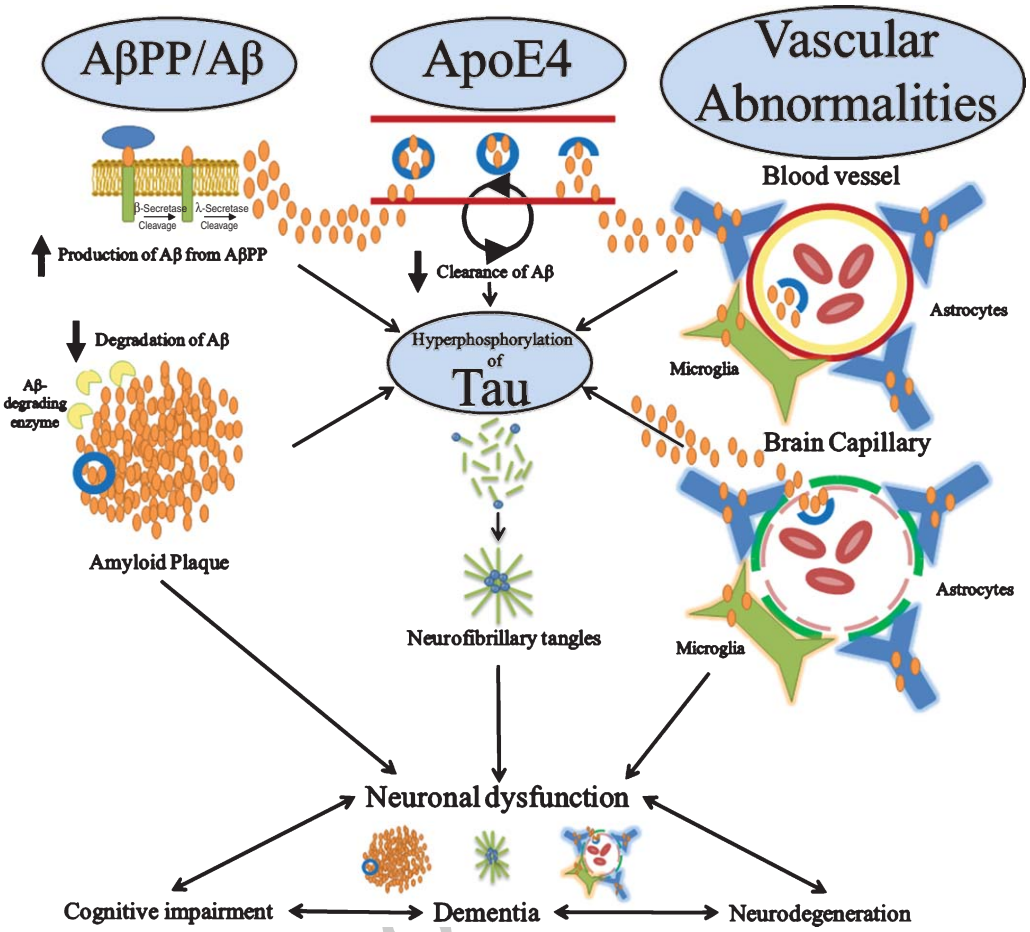

Fig. 1. Hypothetical model of multifactorial Alzheimer's disease (AD) pathogenesis. AD is likely to be caused by interactions among multiple factors, including amyloid-β protein precursor (AβPP)/amyloid-β (Aβ), tau, apolipoprotein E (ApoE4), and vascular abnormalities. Aβ accumulation in brain results from increased Aβ production from AβPP, decreased degradation, or reduced clearance across the dysfunctional blood-brain barrier. Aβ accumulation leads to the formation of Aβ oligomers and amyloid plaques, which are toxic to neurons, whereas its accumulation in the perivascular region leads to cerebral amyloid angiopathy, which disrupts vessel function. Vascular injury also induces toxic accumulation and capillary hypoperfusion, leading to early neuronal dysfunction. Aβ aggregation amplifies neuronal dysfunction, impairs synaptic functions, triggers the release of neurotoxic mediators from microglial cells, and contributes to disease propagation. The lipid transport protein ApoE is primarily synthesized by astrocytes and microglia and once lipidated forms lipoprotein particles. Lipidated ApoE binds soluble Aβ and promotes Aβ uptake through cell-surface receptors or thorough the blood-brain barrier. The ApoE4 isoform impairs Aβ clearance and promotes Aβ deposition. Both Aβ and hypoperfusion can induce tau hyperphosphorylation, leading to neurofibrillary tangle formation.

understood [3]. A system that could be implicated in this relationship between vascular disease and AD is the cholinergic system. The cholinergic system is a crucial regulator of the cardiovascular and autonomic functions, and it is prominently affected in AD, beginning in the pre-clinical phases. Various lines of evidence indicate that in AD the cortical perivascular cholinergic nerve terminals are largely lost, contributing to the impairment of the observed reduction in cerebral blood flow: the analysis of this relationship has also led to the cholinergic-vascular hypothesis [4, 5]. Moreover, various central nervous system structures affected in AD are also implicated in autonomic nervous system regulation, such as hypothalamus, locus coeruleus, cerebral neocortex, insular cortex, and brain stem [6]. Thus, a deficit in central cholinergic function could likely lead to autonomic dysfunction, suggesting that a link between higher cerebral and autonomic neural functions could be reasonably hypothesized in dementia. To date, however, the autonomic involvement in AD has received only limited attention even though its investigation could have important clinical potential, because the recognition of autonomic failure in AD might prevent the disabling complications

Table 1
Autonomic function tests

Test	System explored	Advantages	Disadvantages
Heart Rate Interval Variability	Cardiac sympathovagal balance	Simple, non-invasive	Unknown
Ewing's battery tests	Cardiac sympathovagal balance	Simple, non-invasive	Require some degree of collaboration from the subject
Baroreflex	Baroreflex function	Simple, non-invasive	Unknown
Carotid Sinus Massage	Carotid sinus reflex sensitivity	Simple, non-invasive	Should be avoided in patients with ventricular arrythmia events, recent myocardial infarction or cerebro-vascular events
Plasma epinephrine and norepinephrine measurement	Adrenergic system	Simple, non-invasive	High variability
Cardiac MIBG scintigraphy	Adrenergic innervation of the heart	*In vivo* evaluation of cardiac innervation	Invasive, expensive, available only in specialized centers

of postural dizziness, syncope and falls, which increase the risk of morbidity, institutionalization, and mortality in these individuals [7].

Thus, in this review, we will focus on the principal tests used to evaluate sympathetic and parasympathetic dysfunction, and we will also report the evidence on autonomic dysfunction in AD from the literature.

SYMPATHOVAGAL FUNCTION ASSESSMENT IN AD PATIENTS

The sympathetic and parasympathetic nervous system are key regulators of important functions, as blood pressure (BP), heart rate (HR), respiration, gastrointestinal, endocrine, urinary continence, and sexual function [8, 9]. Several autonomic function tests have been developed in order to investigate the severity and distribution of autonomic dysfunction, to evaluate the orthostatic intolerance, to diagnose the autonomic neuropathy, and to monitor the course of autonomic dysfunction and the response to eventual treatment [8]. Furthermore, autonomic function tests are an important tool in research studies investigating cardiovascular and neurological disease pathophysiology. The central nervous system structures related to the sympathovagal network are hypothalamic structures such as paraventricular nucleus, dorsomedial nucleus, lateral hypothalamic area, posterior hypothalamic nucleus, and mammillary nucleus. These structures control both the sympathetic and parasympathetic outflow. The extra-hypothalamic structures related to sympathetic drive are locus coeroleus, rostral and ventrolateral caudal medulla, and raphe nuclei, with respect to other extra-hypothalamic structures such as dorsal motor nucleus of vagus, amygdala, and nucleus ambygus that control the parasympathetic drive [10]. Several of these structures like hypothalamus, locus coeroleus, and insular cortex are primarily involved in AD, therefore it is reasonable to think that there should be a connection between AD pathogenesis and sympathovagal drive [11]. Here we describe some of the methods used to assess autonomic function in AD (Table 1).

Heart rate interval variability

After the patient stays calm, in a rest supine position for about 10–15 minutes, a continuous electrocardiogram (ECG) is recorded for 5 minutes and both the time-domain indexes and frequency-domain indexes are calculated [12]. Time-domain indexes are a statistical calculation of consecutive R-R intervals. In this case, during the continuous 5 minutes ECG recording all QRS complexes and all normal to normal (NN) intervals are detected. From this information the mean HR, mean NN interval, difference between longer-shorter NN can be calculated. Another statistical variable derived from this analysis is the standard deviation of NN intervals (SDNN). Frequency-domain indexes are a spectral method that analyses the fluctuations in the frequency domain. The average of R-R intervals undergoes Fourier transform algorithm to obtain the power spectral density, so the units of cycles/beat are converted in cycles/s (Hz). From the above calculations low frequency (0.04–0.15 Hz) and high frequency bands (0.15–0.4 Hz) are obtained. The low frequency/high frequency bands ratio is used as a marker of sympathovagal balance. This is a simple, non-invasive method and taking advantage on the little cooperation needed, it can be used even in the advanced stage AD patient [13].

Ewing's battery tests

Five simple, noninvasive cardiovascular reflex tests have been used by Ewing and colleagues to assess autonomic function in diabetic patients [14]. Thereafter,

their use has been widespread in the evaluation of autonomic function in several clinical settings, providing accuracy and reliability in the assessment of the autonomic system. The five tests used in Ewing's standard battery are: the heart rate responses to the Valsalva maneuver, standing up (30:15 ratio), and deep breathing (maximum-minimum heart rate); the BP responses to standing up (postural BP change), and sustained handgrip.

Valsalva ratio

The Valsalva maneuver consists in performing forced expiration for 15 seconds at a pressure of 40 mmHg. The Valsalva ratio is calculated dividing the maximal R-R interval during 15 seconds of expiration by the minimal R–R interval during the maneuver [15].

Heart rate response to standing

Physiologically, after standing an increase in heart rate occurs; this reaches its maximum at about the 15th beat after standing, followed by a relative bradycardia, maximal around the 30th beat. The ratio of maximum R–R interval at the 30th beat to the minimum R–R interval at the 15th beat represents the 30:15 ratio.

R–R interval variation (RRIV) during rest and deep breathing (DB)

This method is also performed by ECG recordings after about 5–10 minutes of rest in supine position [16]. In this position the patient is invited to perform forced DB at 6 breaths/minutes (5 seconds for inspiration and 5 seconds for expiration), controlled by ECG recordings. According to the longest and the shortest R-R interval duration (in rest or during forced DB), the mean R-R is calculated. Difference between longest and shortest R-R interval duration is the average between them. The ratio between mean and average R–R interval is considered as the RRIV. The RRIV at rest is a simple method that can be performed in most of the patients with AD [17]. However, performing this test in advanced stage AD patients can be potentially difficult.

Blood pressure variation (BP)

Orthostatic hypotension is evaluated by monitoring BP in supine position after 10 minutes of rest and then after 3 minutes of active standing position. According to other protocols, BP monitoring is also performed during a) Valsalva maneuver, evaluated as the BP response by the difference between the peak systolic BP during the maneuver and the mean systolic BP prior to the maneuver. The BP behavior during Valsalva maneuver is described in four phases as the act of blowing induces a transient rise in BP (phase I), thereafter the reduced preload manifests as reduced BP (early phase II), this reduction induces a BP rise as a result of baroreflex activation (late phase II); then the patient stops the maneuver and the BP starts falling (phase III), and in the end the vascular peripheral resistance increases and the BP rises (phase IV); b) BP control during isometric exercise (or handgrip): the patient is invited to remain in a sitting position for at least 3 minutes after 10–15 minutes of resting in supine position. In this case the BP response is calculated as difference between the mean diastolic BP prior to sitting position and just before the end of sitting exercise; in the handgrip tests, handgrip is maintained at 30% of the maximum voluntary contraction using a dynamometer for up to 5 minutes. The difference between the diastolic BP just before release of handgrip, and before starting, is taken as the test measure; c) Cold presser test: diastolic BP variation is evaluated after the participant submerges his left hand in cold water at 4°C [18]. According to the Ewing's classification, the subjects cardiovascular autonomic function can be normal (all tests normal or one borderline), early impaired (one of the three heart rate tests abnormal or two borderline), definitely impaired (two or more of the heart rate tests abnormal), severely impaired (two or more of the heart rate tests abnormal plus one or both of the BP tests abnormal or both borderline) or atypical (any other combination). In the Ewing's battery, the heart rate tests better evaluate the parasympathetic function, while the BP tests measure the sympathetic function.

Baroreflex (BR) estimation

BR is the mechanism responsible for BP and HR control. Sudden changes of BP activate the BR and, as a result of sympathovagal activation, HR is modulated in order to restore the BP. BR estimation consists of ECG recordings and BP control at the same time [19]. To study the eventual BR modification in AD the casual ARXAR model has been used, which describes the casual relationship between R–R interval and BP [20].

Carotid sinus (CS) massage

CS reflex sensitivity is measured by the response of HR and BP after 5–10 seconds of CS massage. After 5 seconds, a fall in HR can be noticed and after 20 seconds, a fall in BP is usually found. However this assessment should be avoided in patients

with ventricular arrhythmia events, recent myocardial infarction, or cerebrovascular events [21].

Plasma epinephrine and norepinephrine measurement

The plasmatic level of cathecolamines is evaluated after 30 minutes in resting supine position and after 5 minutes of orthostatic standing. Blood samples should be kept in ice and spun within 1 hour after collection. Plasma should then be stored at -80°C [22]. Plasmatic levels of cathecolamines have been evaluated also during the cold presser test. In the same conditions also the cortisol and ACTH levels have been evaluated [23].

^{123}I-MIBG scintigraphy

Another method to study the sympathetic drive in cardiovascular impairment is iodine-123 meta-iodobenzylguanidine (^{123}I-MIBG) imaging. Non-invasive imaging with iodinated MIBG can assess efferent adrenergic neuronal functions in the heart, as the MIBG competes with noreadrenaline for neuronal uptake. A reduced MIBG uptake has been correlated to sympathetic dysfunction in heart failure and diabetic neuropathy [24, 25]. Recent studies indicate that sympathetic overdrive, represented by reduced MIBG uptake without cardiac pathology involvement, may indicate also a central nervous system involvement [26, 27]. Indeed, it is now established that altered myocardial MIBG uptake can help in the differential diagnosis between Parkinson disease and secondary parkinsonisms, as well as to differentiate between dementia with Lewy body (DLB) and AD [28, 29].

Other methods described in literature for the evaluation of the autonomic function comprise: Holter ECG recording, autonomic urinary test performed by cistometric studies, gastrointestinal test as gastric scintigraphy, thermoregulatory sweat test, phenylephrine and pilocarpine eye drop test.

In summary, we believe that a proper use of the autonomic function test would be not only valuable for the research studies in patients with dementia, but could also bring a benefit to the diagnosis, prognosis and to eventual therapy follow-up.

CLINICAL EVIDENCE ON ALZHEIMER'S DISEASE AND AUTONOMIC DYSFUNCTION

As stated above, autonomic dysfunction, present in all the common dementia subtypes, is believed to be caused by generalized underactivity of the cholinergic system. According to Perry et al. in dementia the parasympathetic and sympathetic systems are affected by a widespread deficit in cholinergic function and all the common subtypes of dementia have been associated with cholinergic deficits [30]. Evidence from previous studies has shown alterations in autonomic modulation in AD, either in terms of impaired vagal parasympathetic function or as altered sympathetic response to orthostasis [17, 22].

Braak suggests a sequence of six stages of AD based on progressive involvement of the two main brain structures implicated in autonomic control, insular cortex, and brainstem. He speculated that these structures may be affected by neurodegeneration in a "preclinical stage" and that the autonomic dysfunction may be present before the onset of clinical symptoms of dementia [6]. Thus, autonomic dysfunction may be a novel biomarker of neurodegeneration. Also Royall et al. suggest that AD is associated with both insular pathology and autonomic dysfunction. Their data indicate that the right hemisphere metabolic changes, showed in the preclinical AD pathology, are significantly associated with mortality in non-demented elderly persons. Furthermore they have measured absolute insular cerebral blood flow (CBF) by dynamic contrast MRI. They noticed that the absolute reductions in right insular CBF and relatively reduced right versus left insular CBF are associated with orthostasis in the same population. These observations indicate that the prevalence of preclinical AD is probably higher than the number of demented cases and that the tests on the right hemisphere functions may be useful in detecting those at risk. Moreover, AD treatment is essential for delaying the progressions of symptoms and might also have an impact on related autonomic dysfunction [31]. In previous reports, cardiac autonomic dysfunction in AD patients, measured by heart rate variability (HRV) assessment, showed a significant correlation with blood levels of acetylcholinesterase activity, suggesting that the presence of autonomic cardiac dysfunction in AD patients might be due to a cholinergic deficit in the peripheral autonomic nervous system [32]. Moreover, autonomic tests have also shown significant correlations with specific neuropsychiatric deficits in AD, hypothesizing that a lack of cortical modulation can play a role [33].

Collins et al. examined dysautonomia in patients with mild cognitive impairment (MCI). MCI represents the earliest clinical stage of AD and other dementias and is characterized by impairment in memory and/or others cognitive domains but preserved

functional abilities [34]. In this study, all subjects underwent Ewing's battery tests to examine the autonomic function and neuropsychological assessment to evaluate the degree of cognitive impairment. MCI patients presented with significant autonomic dysfunction compared with controls. The parasympathetic system was mainly involved in the autonomic dysfunction as demonstrated by the deficits in the HR responses to cardiovascular reflex tests and reduced high frequency on HRV. The predominance of parasympathetic dysfunction in MCI suggests that neurodegeneration may be due to an early cholinergic deficiency that involves central autonomic network in dementia [18].

As previously mentioned, cardiovascular factors are now commonly accepted as risk factors for AD and the BR alterations have been considered as a possible link between BP control and AD [35]. The BR is a reflex loop with cardiac, vascular, and cerebral components involved in a short term BP regulation, acting through the autonomic nervous system by restoring sudden changes in BP through the modulation of heart rate and vascular tone.

Meel-van den Abeelen et al. compared BR function in patients with AD, MCI, and healthy elderly subjects. In AD, the BR was measured in basal conditions and after cholinesterase inhibitors treatment. They found a close relationship between AD and reduced BR function, suggesting that the cholinergic system might play a role. Indeed, cholinesterase inhibitors increased BR function in AD. Moreover, MCI patients showed an intermediate BR function between normal and AD subjects [19].

Van Beek et al. interestingly reported that orthostatic tolerance was preserved in AD, probably due to enhanced sympathetic tone, and galantamine did not affect orthostatic tolerance or HR in AD patients [36]. Moreover, a study investigating the association of the hypotensive syndromes orthostatic hypotension, postprandial hypotension, and carotid sinus hypersensitivity with cognitive impairment has shown that the prevalence of cognitive impairment was similar across the hypotensive syndromes and not significantly different from controls. However, all patients with dementia in this study had higher baseline HR, which could be suggestive of cholinergic function impairment [37].

The majority of studies, using a combination of cardiovascular reflex tests and HRV, reported different modifications of the sympathetic and parasympathetic system in dementia. De Vilhena Toledo and Junqueira evaluated AD subjects with mild to severe cognitive dysfunction, assessed by CAMCOG, the cognitive part of the Cambridge Examination for Mental Disorders, and the Mini-Mental State Examination (MMSE). These patients showed subtle, relative, and absolute depression of parasympathetic modulation and only relative sympathetic over activity [38]. Positive correlations were found between indexes of cardiac parasympathetic modulation of short-term HRV and the cognitive performance assessed by the CAMCOG and MMSE tests scores, while a trend for negative correlation was reported for the sympathetic activity. The authors conclude that the more deficient the cognitive performance, the less is the parasympathetic modulation, and the higher the trend to sympathetic hyperactivity.

Pascualy et al. examined the effects of AD on hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic nervous system responses to a standardized aversive stressor. Subjects included AD and cognitively normal elderly. The authors measured plasma adrenocorticotropin hormone (ACTH), cortisol, norepinephrine, and epinephrine responses to a 1-minute cold pressor test. The cortisol response was increased in the AD group but the ACTH response did not differ between groups. Basal norepinephrine concentrations were higher in the AD group and although norepinephrine responses to cold pressor test did not differ between groups, the BP response was higher in the AD subjects. These results suggest that in AD there is an increased HPA axis responsiveness to cold pressor test at the level of the adrenal cortex and an increase in basal sympathoneural activity and in cardiovascular responsiveness to sympathoneural stimulation [23]. A previous report from our group has also indicated that other possible markers of sympathetic overactivity, as G-protein coupled receptor kinase 2 (GRK2) protein levels in circulating lymphocyte, are upregulated in AD patients with both mild and moderate/severe clinical manifestations of the syndrome and are significantly correlated with the severity of cognitive impairment [39]. In cardiovascular disease, lymphocyte GRK2 protein levels are an emerging biomarker of sympathetic dysfunction with important prognostic implications [40] and several lines of evidence suggest that GRK2 could also play a crucial role in AD-related neurodegeneration [41].

Recent studies have compared the prevalence of autonomic dysfunction in different dementia subtypes. In particular, Allan and colleagues evaluated patients with AD, DLB, vascular dementia (VaD), and Parkinson's disease dementia (PDD). The authors enrolled elderly patient (>65 years) and clinical autonomic function tests were carried out according to Ewing's battery [14]. The results emphasized that there were

important differences between the four types of dementia, with orthostatic hypotension being prevalent in all patients with dementia, implying the need for further research in orthostatic hypotension as a modifiable risk factor for falls in these patients. Indeed, autonomic dysfunction occurred in all subtypes of dementia but was especially noticeable in PDD and DLB with important implications for patient management [15].

In a previous study, Allan and colleagues had also examined the prevalence and severity of autonomic symptoms in patients with different subtypes of dementia and their association with levels of physical activity, activities of daily living, depression, and quality of life. They enrolled patients affected by PDD, DLB, VaD, AD, and healthy controls. They noticed, also in this study, that the autonomic symptoms were significantly higher in PDD, DLB, and VaD patients than either controls or AD patients. Moreover the autonomic symptom scores were associated with poorer outcomes in physical activity, activity of daily living, depression, and quality of life [42].

Recent data point out important therapeutic implications, showing that cholinesterase inhibitors can modulate autonomic function in patients with AD. Indeed, treatment with these drugs was associated with functional improvement of the autonomic nervous system behavior and to a decrease orthostatic BP in AD patients [43].

CONCLUSIONS

As the elderly population grows, the prevalence of patients with dementia will contextually increase, posing a challenge for accurate clinical management not only of the cognitive aspects of these diseases, but also of their associate conditions, among which autonomic dysfunction plays an important role. Autonomic failure may occur as part of the dementing process, as some authors suggest, can be the result of altered response to stress conditions or might be exacerbated by drugs interfering with the autonomic function. Moreover, the existence of modifications of the cardiac sympathovagal balance toward a higher sympathetic and lower parasympathetic modulation are highly prevalent in elderly and may contribute to disrupted homeostatic adaptive capacity. In any case, it is likely to expect a higher proportion of abnormal autonomic manifestations and symptoms in patients with dementia, thus a thorough clinical autonomic assessment for elderly demented patient must be performed, taking advantage of several non-invasive tests available. However, further studies with standard methodologies in larger groups of patients are advisable, in order to improve the benefits of these tests in clinical practice. Moreover, prospective studies are needed, evaluating whether the early detection of autonomic dysfunction in dementia might favorably impact patients clinical management. In addition to that, autonomic derangement itself could be an early biomarker in dementia diagnosis, and could also help in the differential diagnosis among dementia subtypes.

Importantly, the impact of autonomic dysfunction on key symptoms such as dizziness, syncope, falls, constipation, and incontinence needs to be carefully investigated in patients with dementia. Future studies should address whether multi-factorial interventions can improve autonomic function in these patients, improving quality of life and preventing the disabling complications which increase the risk of morbidity, institutionalization, and mortality in these individuals.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2262).

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